PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 532-113 PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CA 03/01284	International filing date *(day/month/year)* 02.09.2003	Priority date *(day/month/year)* 30.08.2002
International Patent Classification (IPC) or both national classification and IPC A61K35/78		
Applicant BIOPHARMACOPAE DESIGN INTERNATIONAL INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.03.2004	27.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Laffargue-Haak, T Telephone No. +49 89 2399-8009

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA 03/01284

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-241 as originally filed

Claims, Numbers

1-51 received on 08.11.2004 with letter of 08.11.2004

Drawings, Sheets

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-24

   because:

   ☒ the said international application, or the said claims Nos. 1-19 (IA only) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☒ the claims, or said claims Nos. 1-24 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-24
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-24
Industrial applicability (IA)	Yes:	Claims	1-9, 20-24 ; 10-19 : see separate sheet

No: Claims

2. Citations and explanations

see separate sheet

I Basis of the report

The amended claims 1-51, filed on 08.11.2004, introduce subject-matter going beyond the disclosure as originally filed (Art. 34(2)(b) PCT). There is no basis for replacing "sub-library of plant extracts" by "library of plants" (cf new claims 10-16, 20, 34). Furthermore, there is no basis in the application as originally filed for the features of new claim 10, step(c) wherein the plant material is subjected to **three or more sequential** extraction processes. The applicant's assertion that "support for the new claims can be found throughout the specification as originally filed" is of no help, taking into account the 241 pages of description. Consequently, the present opinion is based on the application documents as originally filed.

III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 10-19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Present claims 1-24 relate to an extremely large number of possible extracts, uses and processes. Basically any extract obtained from any plant by any type of extraction process that inhibits extracellular protease and has some effect on the migration of endothelial and/or neoplastic cells, irrespective of the fact whether the effect has been explicitly disclosed or not (e.g. those disclosed on p.3, l. 10-23 of the present description), is novelty destroying for independent product claims 1, 4, 9 and 24. The same holds for the process claims 20 and 22. The discovery of one or more functional features cannot confer novelty to a product per se.

V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

Novelty

Product claims

Independent claims 1, 4, 24 and 9 relate to plant extracts which are characterised by two functional features, namely the fact that they (i) inhibit at least one extracellular protease and (ii) the migration of endothelial and/or neoplastic cells. Thus, any type of plant extract which has these properties, is novelty destroying, irrespective whether this effect is explicitly disclosed or not (see point III).

For instance, D1-D5 (see passages of the ISR) all disclose plant extracts which all inhibit extracellular protease and are thus novelty destroying for product claims 1-9 and 24.

Present claims 4 and 24 are so-called product-by-process claims. These claims are product claims for which the process features are not limiting. Novelty can thus not be derived from these features.

Process claims

Claims 20-23 relate to processes for selecting plant extracts which share the two above mentioned functional features, namely inhibition of extracellular protease and inhibition of endothelial or neoplastic cell migration. These processes are characterised merely by a first step to establishing the inhibition of extracellular protease, followed by a second step to determine the cell migration inhibition.

The extracts disclosed in D1-D5 were necessarily subjected to such generic processes as claimed in claims 20-23 and these claims are thus already anticipated by these disclosures.

Use claims

Claims 10-19 relate to the second medical use of plant extracts of claims 1-3 for the treatment of either angiogenesis or metastasis. D1-D4 clearly disclose the relationship between inhibition of extracellular protease and angiogenesis/metastasis and these disclosures are thus also novelty destroying for present claims 10-19.

Inventive step

The question whether the claimed invention is based on inventive step only arises if there is novelty. As explained above, this does not seem be case.

For the sake of completeness, it would appear that the contribution made to art by the present patent application, as based on the application documents as a whole, lies in the establishment of a library of plant extracts, which show the inhibition of extracellular protease and cell migration. A mere juxtaposition of features (i.e. plant extracts) without any functional relationship between the feature of a combination (i.e. library of plant extracts) can never involve an inventive step.

Industrial applicability

For the assessment of the present claims 10-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VI Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 03/035092	*01-05-2003*	*25-10-2002*	*26-10-200*

VII Certain defects in the international application

Relevant background art is not cited in the descriptions and the requirements of Rule 5.1(a)(ii) PCT are therefore not fulfilled.

VIII Certain observations on the international application

Claim 1 is not clear as the expression "MMP" should be written in full (i.e. matrix metalloprotease (Art. 6 PCT).

It is unclear what is meant by the expression "a sub-library of plant extracts" of claim 4 (Art. 6 PCT). It is assumed that it is to be understood as a plurality of plant extracts.

Claim 12 is not clear, as it lacks an essential feature, namely the disease to be treated. This also holds for claim 15, which relates to "migration of endothelial or neoplastic cells". These features relate to a mechanism of action and not a disease (Art. 6 P PCT).

The claims lack conciseness as a whole, as there are four independent product claims, four independent use claims and two independent process claims (Art. 6 PCT).

Cited documents

Documents of the international search report are numbered according to the order of appearance :

D1: WO 02/11745 A (KIM MIN YOUNG ; ANGIOLAB INC (KR); MOON CHANG HEE (KR); PARK EUN KYU () 14 February 2002 (2002-02-14)

D2: WO 00/62789 A (PHARMASCIENCE LAB ; PAUL FRANCOIS (FR); MSIKA PHILIPPE (FR); PICCIRILL) 26 October 2000 (2000-10-26)

D3: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 31 July 1996 (1996-07-31), KUMAGAI, KAZUO ET AL: "Flavones or anthocyanins as matrix metalloprotease inhibitors and their extraction from medicinal plants for therapeutic use" XP002266822 retrieved from STN Database accession no. 125:67741

D4: PAPER D H: "NATURAL PRODUCTS AS ANGIOGENESIS INHIBITORS" PLANTA MEDICA, THIEME, STUTTGART, DE, vol. 64, no. 8, December 1998 (1998-12), pages 686-695, XP001023843 ISSN: 0032-0943

D5: LEE, K.-K. ET AL: "Inhibitory effects of 150 plant extracts on elastase activity, and their anti-inflammatory effects." INTERNATIONAL JOURNAL OF COSMETIC SCIENCE, (APRIL, 1999) VOL. 21, NO. 2, PP. 71-82. PRINT. CODEN: IJCMDW. ISSN: 0142-5463., 1999, XP002266821

D6: WO 03/035092 A (KIM KYOUNG-MI ; KIM MIN-YOUNG (KR); ANGIOLAB INC (KR); MOON CHANG-HEE) 1 May 2003 (2003-05-01)

D7: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 7 August 2003 (2003-08-07), INOMATA, SHINJI ET AL: "MMP inhibitors and skin preparations containing plant

(extracts)" XP002266823 retrieved from STN Database accession no. 139:106121

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A plant extract that inhibits the activity of at least one extracellular protease selected from the group of: matrix metalloprotease-1 (MMP-1), matrix metalloprotease-2 (MMP-2), matrix metalloprotease-3 (MMP-3), matrix metalloprotease-9 (MMP-9), and cathepsin B, said extract having at least one of the following properties:

   (i) is capable of slowing down or inhibiting migration of endothelial cells, and

   (ii) is capable of slowing down or inhibiting migration of neoplastic cells,

   with the proviso that said extract is derived from a plant other than *Ginkgo biloba* or *Lupinus albus*.

2. A plant extract that inhibits the activity of at least one extracellular protease selected from the group of: matrix metalloprotease-1 (MMP-1), matrix metalloprotease-2 (MMP-2), matrix metalloprotease-3 (MMP-3), matrix metalloprotease-9 (MMP-9), and cathepsin B, said extract having at least one of the following properties:

   (i) is capable of slowing down or inhibiting migration of endothelial cells, and

   (ii) is capable of slowing down or inhibiting migration of neoplastic cells,

   wherein said extract is derived from a plant that has been subjected to one or more stress.

3. The plant extract according to claim 2, wherein said stress is a chemical stress.

4. The plant extract according to any one of claims 1 to 3, wherein said extract is derived from any one of the plants listed in Table 1, 2, 3, 4 or 5.

5. The plant extract according to any one of claims 1 to 3, wherein said extract is derived from any one of the plants listed in Table 13 or 14.

6. The plant extract according to any one of claims 1 to 3, wherein said extract is selected from any one of the extracts listed in Table 13 or 14.

7. The plant extract according to any one of claims 1 to 6, wherein said extract is prepared by extraction using an alcoholic or aqueous solvent.

8. The plant extract according to any one of claims 1 to 7, wherein said extract inhibits the activity of said at least one extracellular protease by at least 20%.

9. The plant extract according to any one of claims 1 to 7, wherein said extract inhibits the activity of said at least one extracellular protease by at least 50%.

10. A library of plant extracts capable of slowing down or inhibiting cell migration that are suitable for use in the preparation of pharmaceutical compositions for inhibition or prevention of angiogenesis and/or metastasis, said library being prepared by a process comprising:

(a) selecting a group of plants;

(b) harvesting plant material from each plant in said selected group of plants;

(c) subjecting said plant material from each plant to three or more sequential extraction processes utilising different solvents to provide a plurality of potential extracts;

(d) analysing each potential extract for inhibitory activity against at least one extracellular protease;

(e) selecting those potential extracts that are capable of inhibiting the activity of at least one extracellular protease to provide a group of extracts;

(f) analysing the ability of each extract in said group of extracts to slow down or inhibit migration of endothelial and/or neoplastic cells *in vitro*, and

(g) selecting those extracts that are capable of slowing down or inhibiting migration of endothelial and/or neoplastic cells to provide said library of plant extracts.

11. The library according to claim 10, wherein said process further comprises subjecting said selected group of plants to one or more stress prior to harvesting said plant material.

12. The library according to claim 10 or 11, wherein step (d) comprises selecting those potential extracts that are capable of inhibiting the activity of at least one extracellular protease by 20% or more.

13. The library according to any one of claims 10 to 12, wherein step (f) comprises selecting those extracts that are capable of slowing down or inhibiting migration of said endothelial and/or neoplastic cells by at least 10% when compared to untreated control cells.

14. A library of plant extracts suitable for use in the preparation of pharmaceutical compositions for the inhibition or prevention of angiogenesis and/or metastasis, each of said plant extracts being capable of inhibiting the activity of at least one extracellular protease and having at least one of the following properties: (i) is capable of slowing down or inhibiting migration of endothelial cells, and (ii) is capable of slowing down or inhibiting migration of neoplastic cells.

15. The library according to any one of claims 10 to 14, wherein said at least one extracellular protease is selected from the group of: matrix metalloprotease-1 (MMP-1), matrix metalloprotease-2 (MMP-2), matrix metalloprotease-3 (MMP-3), matrix metalloprotease-9 (MMP-9), and cathepsin B.

16. The library according to any one of claims 10 to 15, wherein said library comprises plant extracts derived from the plants listed in any one of Tables 1, 2, 3, 4 or 5, or a combination thereof.

17. A pharmaceutical composition comprising the plant extract according to any one of claims 1 to 9 and a pharmaceutically acceptable diluent, excipient or carrier.

18. A formulation comprising the plant extract according to any one of claims 1 to 9 and a physiologically acceptable diluent, excipient or carrier.

19. Use of the plant extract according to any one of claims 1 to 9 to slow down, inhibit or prevent angiogenesis in an animal in need thereof.

20. Use of a plant extract that inhibits the activity of at least one extracellular protease selected from the group of: matrix metalloprotease-1 (MMP-1), matrix metalloprotease-2 (MMP-2), matrix metalloprotease-3 (MMP-3), matrix metalloprotease-9 (MMP-9), and cathepsin B, and has at least one of the following properties:

(i) is capable of slowing down or inhibiting migration of endothelial cells, and

(ii) is capable of slowing down or inhibiting migration of neoplastic cells,

to slow down, inhibit or prevent metastasis in an animal in need thereof, with the proviso that said extract is derived from a plant other than *Ginkgo biloba*.

21. Use of a plant extract that inhibits the activity of at least one extracellular protease selected from the group of: matrix metalloprotease-1 (MMP-1), matrix metalloprotease-2 (MMP-2), matrix metalloprotease-3 (MMP-3), matrix metalloprotease-9 (MMP-9), and cathepsin B, and has at least one of the following properties:

(i) is capable of slowing down or inhibiting migration of endothelial cells, and

(ii) is capable of slowing down or inhibiting migration of neoplastic cells,

to slow down, inhibit or prevent metastasis in an animal in need thereof, wherein said extract is derived from a plant that has been subjected to one or more stress.

22. Use of the plant extract according to any one of claims 1 to 9 in the manufacture of a medicament for inhibition or prevention of angiogenesis in an animal in need thereof.

23. Use of a plant extract that inhibits the activity of at least one extracellular protease selected from the group of: matrix metalloprotease-1 (MMP-1), matrix metalloprotease-2 (MMP-2), matrix metalloprotease-3 (MMP-3), matrix metalloprotease-9 (MMP-9), and cathepsin B, and has at least one of the following properties:

(i) is capable of slowing down or inhibiting migration of endothelial cells, and

(ii) is capable of slowing down or inhibiting migration of neoplastic cells,

in the manufacture of a medicament for inhibition or prevention of metastasis in an animal in need thereof,

with the proviso that said extract is derived from a plant other than *Ginkgo biloba*.

24. Use of a plant extract that inhibits the activity of at least one extracellular protease selected from the group of: matrix metalloprotease-1 (MMP-1), matrix metalloprotease-2 (MMP-2), matrix metalloprotease-3 (MMP-3), matrix metalloprotease-9 (MMP-9), and cathepsin B, and has at least one of the following properties:

(i) is capable of slowing down or inhibiting migration of endothelial cells, and

(ii) is capable of slowing down or inhibiting migration of neoplastic cells,

in the manufacture of a medicament for inhibition or prevention of metastasis in an animal in need thereof, wherein said extract is derived from a plant that has been subjected to one or more stress.

25. Use of the plant extract according to any one of claims 1 to 9 to slow down cell migration in an animal in need thereof.

26. The use according to claim 25, wherein said cell migration is endothelial cell migration.

27. The use according to claim 26, wherein said endothelial cell migration is associated with angiogenesis.

28. The use according to claim 25, wherein said cell migration is neoplastic cell migration.

29. The use according to claim 28, wherein said neoplastic cell migration is associated with metastasis.

30. A process for preparing a library of plant extracts capable of slowing down or inhibiting cell migration that are suitable for use in the preparation of pharmaceutical compositions for inhibition or prevention of angiogenesis and/or metastasis, said process comprising:

(a) selecting a group of plants;

(b) harvesting plant material from each plant in said selected group of plants;

(c) subjecting said plant material from each plant to three or more sequential extraction processes utilising different solvents to provide a plurality of potential extracts;

(d) analysing each potential extract for inhibitory activity against at least one extracellular protease;

(e) selecting those potential extracts that are capable of inhibiting the activity of at least one extracellular protease to provide a group of extracts;

(f) analysing the ability of each extract in said group of extracts to slow down or inhibit migration of endothelial and/or neoplastic cells *in vitro*, and

(g) selecting those extracts that are capable of slowing down or inhibiting migration of endothelial and/or neoplastic cells to provide said library of plant extracts.

31. The process according to claim 30, further comprising the steps of subjecting each plant extract in said group of extracts to at least one cytotoxicity, bioavailability or stability test and selecting those extracts that demonstrate physiologically acceptable cytotoxicity, bioavailability and/or stability.

32. The process according to claim 30 or 31, further comprising subjecting said selected group of plants to one or more stress prior to harvesting said plant material.

33. The process according to any one of claims 30 to 32, wherein said at least one extracellular protease is selected from the group of: matrix metalloprotease-1 (MMP-1), matrix metalloprotease-2 (MMP-2), matrix metalloprotease-3 (MMP-3), matrix metalloprotease-9 (MMP-9), and cathepsin B.

34. A library of plant extracts prepared by the process according to any one of claims 30 to 33.

35. A process for identifying a plant extract capable of slowing down or inhibiting cell migration that is suitable for use in the preparation of a pharmaceutical composition for inhibition or prevention of angiogenesis and/or metastasis, said process comprising:

(a) selecting a group of plants;

(b) harvesting plant material from each plant in said selected group of plants;

(c) subjecting said plant material from each plant to three or more sequential extraction processes utilising different solvents to provide a plurality of potential extracts;

(d) analysing each potential extract for inhibitory activity against at least one extracellular protease;

(e) selecting those potential extracts that are capable of inhibiting the activity of at least one extracellular protease to provide a group of plant extracts;

(f) analysing the ability of each plant extract in said group of plant extracts to slow down or inhibit migration of endothelial and/or neoplastic cells *in vitro*, and

(g) selecting a plant extract that is capable of slowing down or inhibiting migration of said endothelial and/or neoplastic cells.

36. The process according to claim 35, further comprising the steps of subjecting each plant extract in said group of plant extracts to at least one cytotoxicity, bioavailability or stability test and selecting an extract that demonstrates physiologically acceptable cytotoxicity, bioavailability and/or stability.

37. The process according to claim 35 or 36, wherein said at least one extracellular protease is selected from the group of: matrix metalloprotease-1 (MMP-1), matrix metalloprotease-2 (MMP-2), matrix metalloprotease-3 (MMP-3), matrix metalloprotease-9 (MMP-9), and cathepsin B.

38. The process according to any one of claims 35 to 37, further comprising subjecting said selected group of plants to one or more stress prior to harvesting said plant material.

39. A plant extract produced by the process according to any one of claims 35 to 38, with the proviso that said extract is derived from a plant other than *Ginkgo biloba* or *Lupinus albus*.

40. A plant extract produced by the process according to claim 38.

41. A process for preparing a pharmaceutical composition for the inhibition or prevention of angiogenesis and/or metastasis, said process comprising:

(a) selecting a group of plants;

(b) harvesting plant material from each plant in said selected group of plants;

(c) subjecting said plant material from each plant to three sequential extraction processes utilising different solvents to provide a plurality of potential extracts;

(d) analysing each potential extract for inhibitory activity against at least one extracellular protease;

(e) selecting those potential extracts that are capable of inhibiting the activity of at least one extracellular protease to provide a group of extracts;

(f) analysing the ability of each extract in said group of extracts to slow down or inhibit migration of endothelial and/or neoplastic cells *in vitro*;

(g) selecting those extracts that are capable of slowing down or inhibiting migration of endothelial and/or neoplastic cells to provide a library of plant extracts;

(h) subjecting said library of extracts to at least one cytotoxicity, bioavailability or stability test;

(i) selecting an extract that demonstrates physiologically acceptable cytotoxicity, bioavailability and/or stability, and

(j) formulating said extract to provide said pharmaceutical composition.

42. The process according to claim 41, further comprising subjecting said selected group of plants to one or more stress prior to harvesting said plant material.

43. The process according to claim 41 or 42, wherein said at least one extracellular protease is selected from the group of: matrix metalloprotease-1 (MMP-1), matrix metalloprotease-2 (MMP-2), matrix metalloprotease-3 (MMP-3), matrix metalloprotease-9 (MMP-9), and cathepsin B.

44. The process according to any one of claims 41 to 43, wherein said pharmaceutical composition is formulated for systemic administration.

45. A pharmaceutical composition produced by the process according to any one of claims 41 to 44.

46. A method of preparing a pharmaceutical composition for the inhibition or prevention of angiogenesis and/or metastasis comprising:

(a) selecting a plant extract from the library of plant extracts according to any one of claims 10, 11, 12, 13, 14, 15, 16 or 34, and

(b) formulating said plant extract to provide a pharmaceutical composition.

47. The method according to claim 46, wherein said pharmaceutical composition is formulated for systemic administration.

48. A plant extract formulated for use as a medicament for the inhibition or prevention of angiogenesis, wherein said plant extract inhibits the activity of at least one extracellular protease and has at least one of the following properties:

(i) is capable of slowing down or inhibiting migration of endothelial cells, and

(ii) is capable of slowing down or inhibiting migration of neoplastic cells,

with the proviso that said extract is derived from a plant other than *Ginkgo biloba* or *Lupinus albus*.

49. A plant extract formulated for use as a medicament for the inhibition or prevention of metastasis, wherein said plant extract inhibits the activity of at least one extracellular protease and has at least one of the following properties:

(i) is capable of slowing down or inhibiting migration of endothelial cells, and

(ii) is capable of slowing down or inhibiting migration of neoplastic cells,

with the proviso that said extract is derived from a plant other than *Ginkgo biloba*.

50. A plant extract formulated for use as a medicament for the inhibition or prevention of angiogenesis and/or metastasis, wherein said plant extract inhibits the activity of at least one extracellular protease and has at least one of the following properties:

(i) is capable of slowing down or inhibiting migration of endothelial cells, and

(ii) is capable of slowing down or inhibiting migration of neoplastic cells,

wherein said extract is derived from a plant that has been subjected to one or more stress.

51. The plant extract according to any one of claims 48 to 50, wherein said at least one extracellular protease is selected from the group of: matrix metalloprotease-1 (MMP-1), matrix metalloprotease-2 (MMP-2), matrix metalloprotease-3 (MMP-3), matrix metalloprotease-9 (MMP-9), and cathepsin B.